Ketones for Healthy Longevity

Ben Best

Pharmacy (BSc Pharm)

Physics/Computing Science (BSc)

Employee – Biomedical Research & Longevity Society

Presentation Outline

- (1) Ketogenic Diet Benefits
- (2) Ketones: Chemistry, Biochemistry, and Physiology
- (3) Exogenous Ketones

Ketogenic Diet Benefits

Ketogenic Diet For Epilepsy

- Ketogenic diet developed as a treatment of last resort for drug resistant epilepsy cases, especially in children
  - 80-90% fat, minimal carbohydrate
    - **Carbohydrate** means sugar or starchy food (not fiber)
    - **Ketogenic** means fats converted to ketones as a source of energy
  - JOURNAL OF CHILD NEUROLOGY 24:979 (2009)

Ketogenic Diet For Other Diseases

- Nearly all **cancer** cells depend on glucose (from carbohydrate). A ketogenic diet starves cancer cells, slowing cancer growth
  - NUTRITION & METABOLISM 7:7 (2010)
- Ketones can enter neurons directly, without the need of insulin, protecting from neurodegeneration
  - JOURNAL OF NUTRITION AND METABOLISM 2018:7195760 (2018)
- Insulin resistant neurons starved for glucose implicated in **Alzheimer's** and other neurodegenerative diseases. Ketones instead of glucose can supply energy to neurons
  - ENDOCRINOLOGY 152:3638 (2011)
- Diabetics on a ketogenic diet show reduced

Ketogenic (Low Carbohydrate) Diet Benefits

- Carbohydrates promote lipid synthesis in the liver, raising blood triglycerides more than dietary fat
  - JOURNAL OF CLINICAL NUTRITION 97:2081 (1996)
  - AMERICAN JOURNAL OF CLINICAL NUTRITION 71:412 (2000)
  - FRONTIERS IN NUTRITION 9:861664 (2022)
- High levels of triglycerides in the bloodstream leads to insulin resistance and diabetes
  - INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES 21:6358 (2020)
- High carbohydrate intake from starchy foods increased visceral fat, blood triglycerides, and metabolic syndrome
  - SCIENTIFIC REPORTS 5:16919 (2015)
- High blood sugar from carbohydrates increases free radical production in mitochondria
  - ARCHIVES OF CARDIOVASCULAR DISEASE 113:736 (2020)

Ketogenic Diet for Longer Healthspan

- A ketogenic diet increased median lifespan, slowed cognitive decline, and preserved motor function in mice
  - CELL METABOLISM 26:539 (2017)
- A ketogenic diet reduced mid-life mortality and improved memory in aging mice
  - CELL METABOLISM 26:547 (2017)
- A ketogenic diet has been shown to protect mice from coronavirus
  - ELIFE 10:e66522 (2021)

Unhealthy Ketogenic Diet Practices

- Many people on a ketogenic diet think fried bacon and other fatty meats are health food
- Advanced Glycation End-Products (AGEs) are formed from sugar, fats, and proteins exp

FOOD	AGEs (kU/100 grams)
Fried Bacon	91,577
Roasted Chicken	18,520
Fried Beef Steak	10,058
Roasted Walnuts	7,887
Grilled Carrots	226
Canned Carrots	10

- AGEs cause inflammation and oxidative stress
- AGEs lead to diabetes, kidney disease,

Animal versus Plant Fats

- Saturated (animal) fat raises liver triglycerides increasing insulin resistance
  - NATURE REVIEWS: GASTROENTEROLOGY & HEPATOLOGY 18:770 (2021)
- Saturated (animal) fats increase intestinal permeability (leaky gut)
  - THE BRITISH JOURNAL OF NUTRITION 124:654 (2020)
- Animal fats are toxic to the insulin-producing cells of the pancreas (leading to diabetes)
  - JOURNAL OF MOLECULAR BIOLOGY 432:1514 (2020)
  - JOURNAL OF POPULATION THERAPEUTICS & CLINICAL PHARMACOLOGY 27:e22 (2020)

Persistent Organic Toxins in Fatty Food

- Many organic pollutants are persistent in the environment, including both pesticides and industrial chemicals: PolyChlorinated Biphenyls (PCBs), organochlorine pesticides, digoxins, lindane, bisphenol A, phtalates, etc.
- Persistent organic chemicals accumulate in the fats of the animals we eat, and thus accumulate even more in our fat
- Pesticides are usually neurotoxic to insects, and to us
- Pesticide exposure can increase the risk of Parkinson's Disease up to 7-fold
  - ENVIRONMENTAL HEALTH PERSPECTIVES 112:950 (2004)

Toxins in Meat

- Nitrates in processed meats (sausages,salami,bacon) have been shown to cause insulin resistance and atherosclerosis. Red meat increases risk of ischemic stroke.
  - PNAS 75:233 (2017)
- TMAO (TriMethylAmine N-Oxide, unpleasant odor of rotting fish) contributes to atherosclerosis. Intestinal microbiota produce TMAO from meat in meat-eaters, but not in vegetarians who are experimentally fed meat.
  - NATURE MEDICINE 19:576 (2013)
- DDT was banned in the US in 1972, PCBs (PolyChlorinated Biphenyls) were banned in 1979, but harmful pesticide use continues and these organic substances persist in fat tissue of animals and bioaccumulate in the fat of humans that eat meat
- PCBs substantially increase TMAO formation in the

Healthy Ketogenic Diet Practices

- Avoiding carbohydrates should not mean avoiding fiber
- Dietary fiber can be transformed into the beneficial short-chain fatty acid **butyrate** in the colon
  - Butyrate is the main energy source for colon cells
- Dietary fiber reduces the risk of obesity and insulin resistance
- Dietary fiber reduces the risk of colon cancer
  - NUTRIENTS 9:1348 (2017)
- Mice with extended healthspan on a ketogenic diet have not been dining on Kentucky Fried Chicken (AGEs)

Healthy Ketogenic Diet Practices

- Get fat (and protein) from plants not animals
  - Olive oil
  - Avocado
  - Nuts
  - Seeds
- Eat high-fiber foods (with healthy oils)
  - Avocado
  - Broccoli
  - Cauliflower
  - Leafy Greens
  - Lentils and other beans

89,224 California Seventh-Day Adventists

American Journal of Clinical Nutrition 89:1607S (2009)

DIET	BMI	DIABETES	HYPERTENSION
Omnivores	28.26	1.00	1.00
Pesco (Fish)-eating Vegetarian	25.73	0.49	0.62
Lacto-ovo Vegetarian	25.48	0.39	0.45
Vegan (no daiiry)	23.13	0.22	0.25

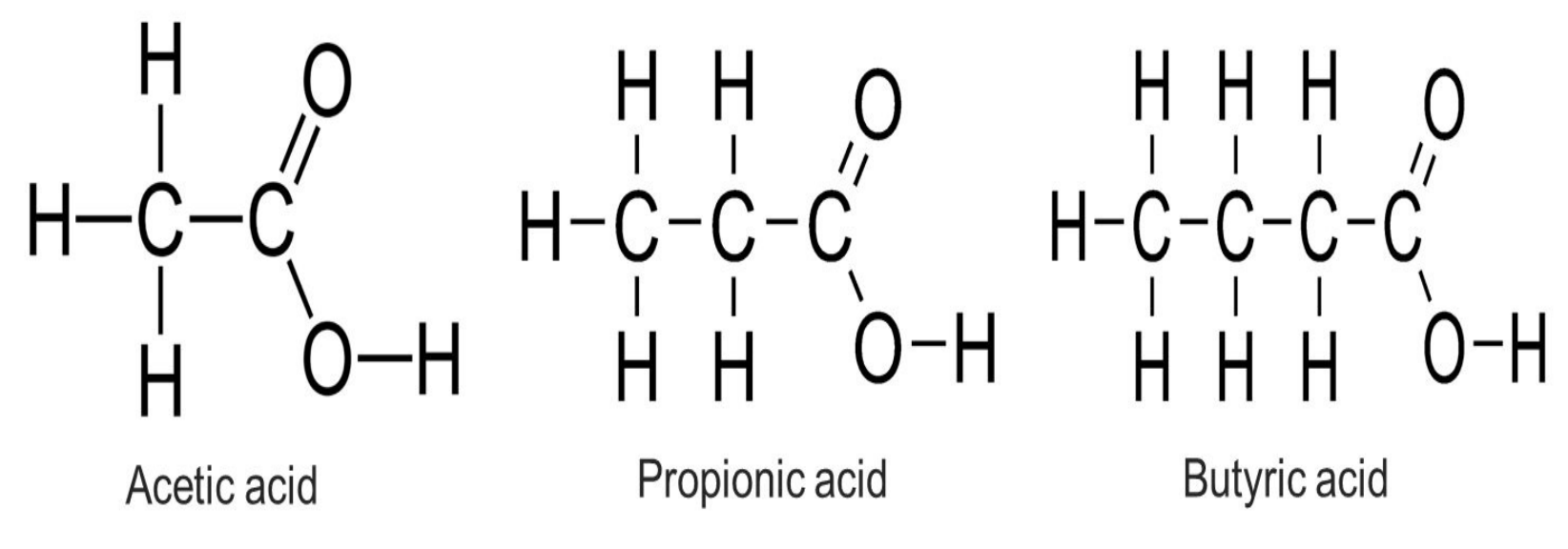
Seventh-Day Adventists US & Canada

NUTRIENTS 6:2131 (2014)

CAUSE OF DEATH	OMNIVORES	VEGETARIANS
CARDIOVASCULAR		
Male	1.00	0.71
Female	1.00	0.99
CANCER	1.00	0.92
ALL CAUSES		
Male	1.00	0.82
Female	1.00	0.93

Ketones: Chemistry, Biochemistry, and Physiology

Short-Chain Fatty Acids (SCFAs)

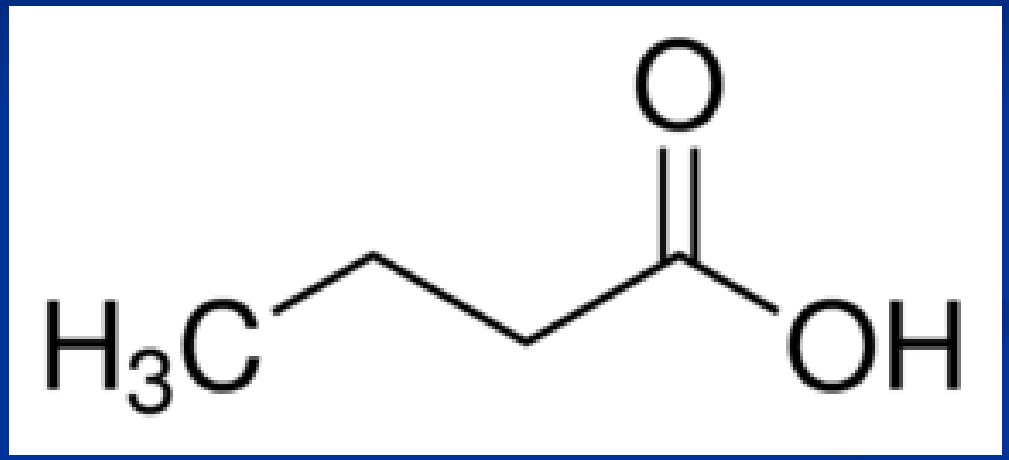


- Acetic acid (acetate) and propionic acid (propionate) are mostly absorbed into the bloodstream, but butyric acid (butyrate) mostly remains in the colon, providing 70% of energy for colon cells
  - INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES 20:1214 (2019)
- Colon cancer cells use glucose, not butyrate for energy, so the excess butyrate modifies gene expression

Short-Chain Fatty Acid (SCFA) benefits

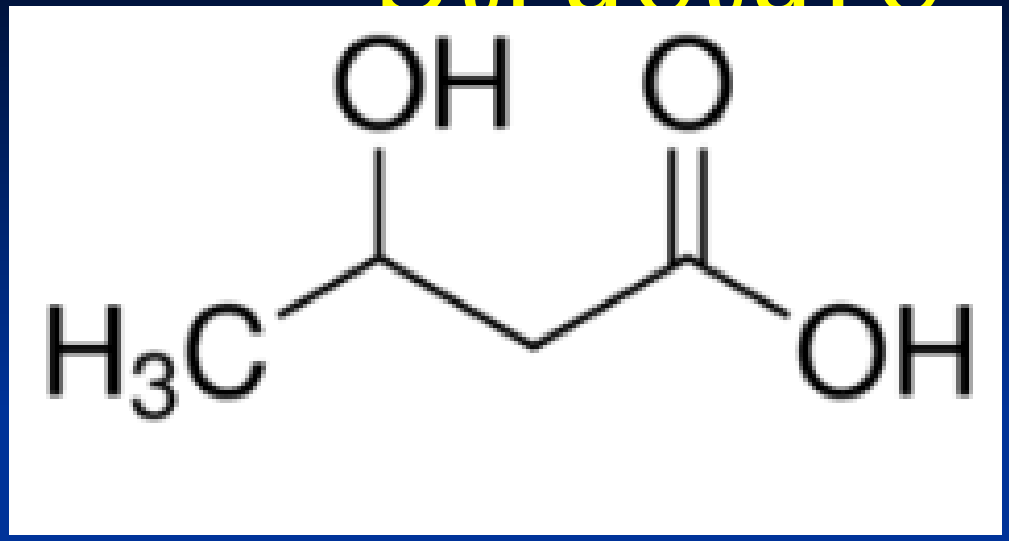
- SCFAs can inhibit inflammatory cytokines and lower blood pressure
  - INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES 21:6356 (2020)
- Butyrate induces the secretion of the hormones GLP-1 and PYY, reducing appetite and increasing insulin sensitivity
  - MOLECULES 26:682 (2021)
- SCFAs, especially butryrate, increase colon mucin and tight-junction proteins, improving intestinal barrier (preventing “leaky gut”)
  - NUTRIENTS 10:1499 (2018)
- Rats fed resistant starch had increased SCFA and 33% life extension
  - BRITISH JOURNAL OF NUTRITION 100:1192 (2008)
- Elderly humans fed resistant starch for three months

Butyric Acid (Butyrate) Structure (short-chain fatty acid produced in the colon from fiber)



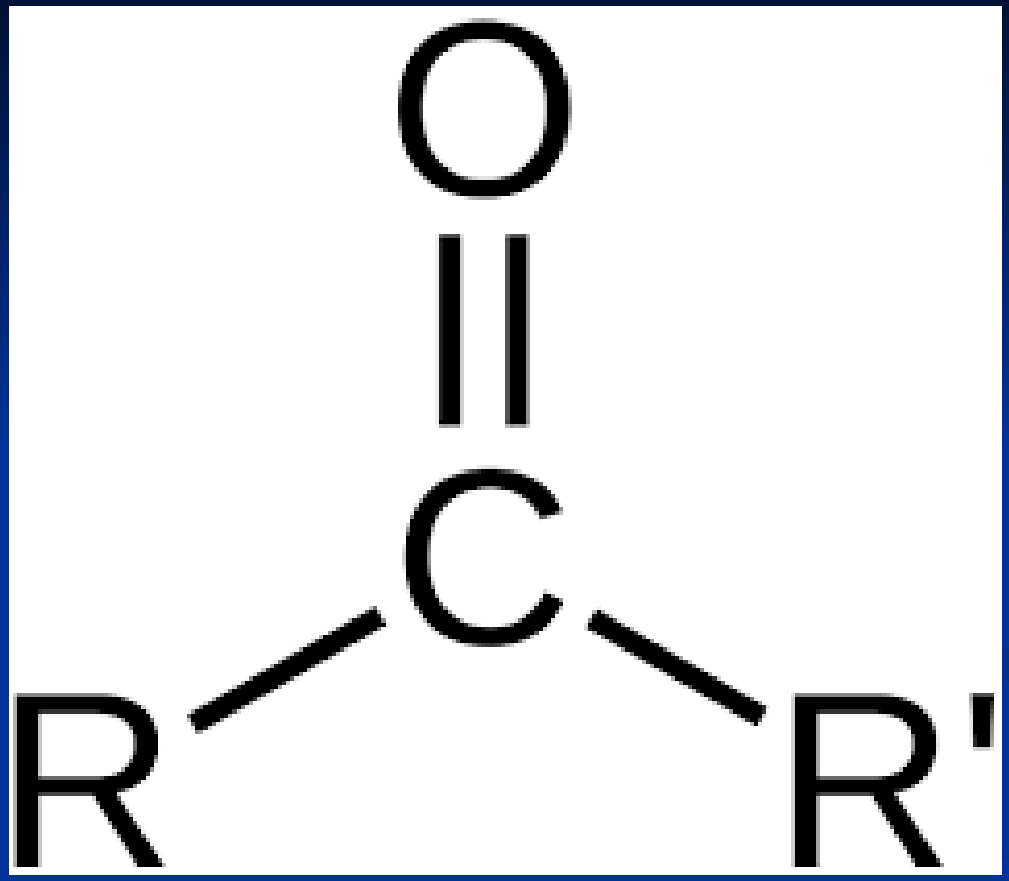
- Conventional stick-figure with Carbon atoms as corners and Hydrogen atoms hidden

Beta-hydroxybutyrate (βHB) Structure



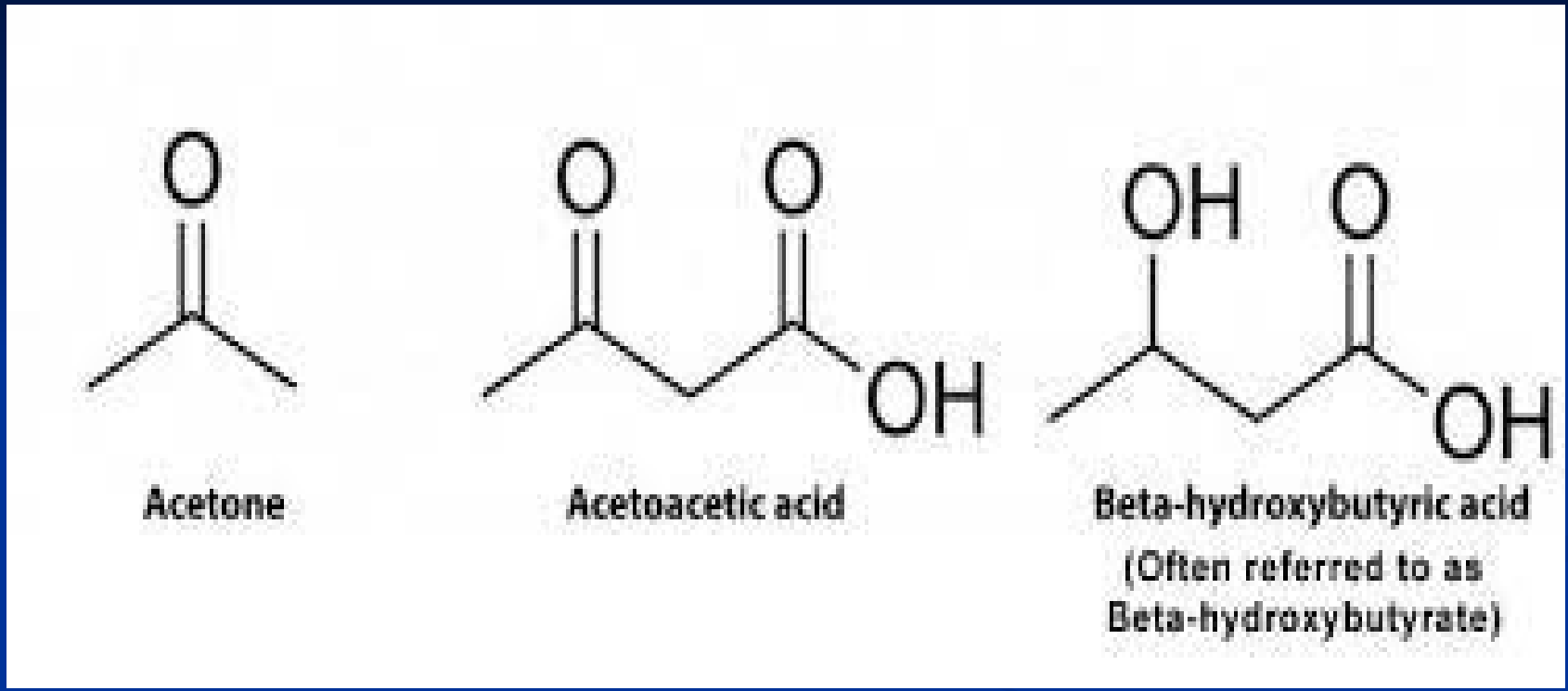
- -OH (hydroxyl) in the beta position
- The main “ketone body” in the blood stream

Ketone Structure



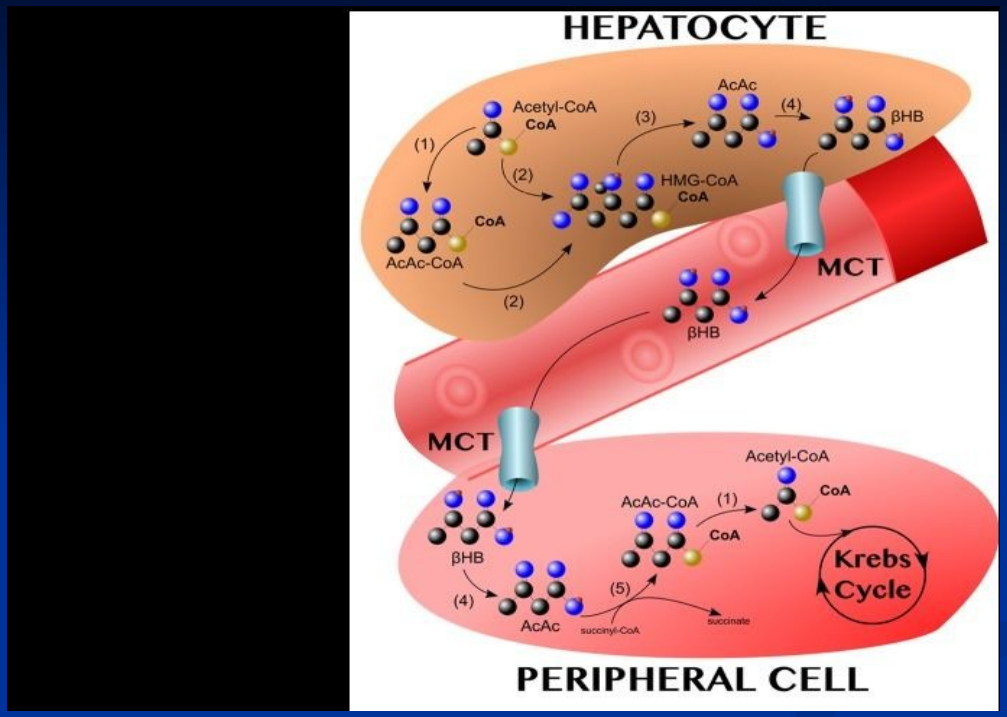
- Carbon and Oxygen atoms shown, organic groups shown as R and R’

The Three Biological Ketones



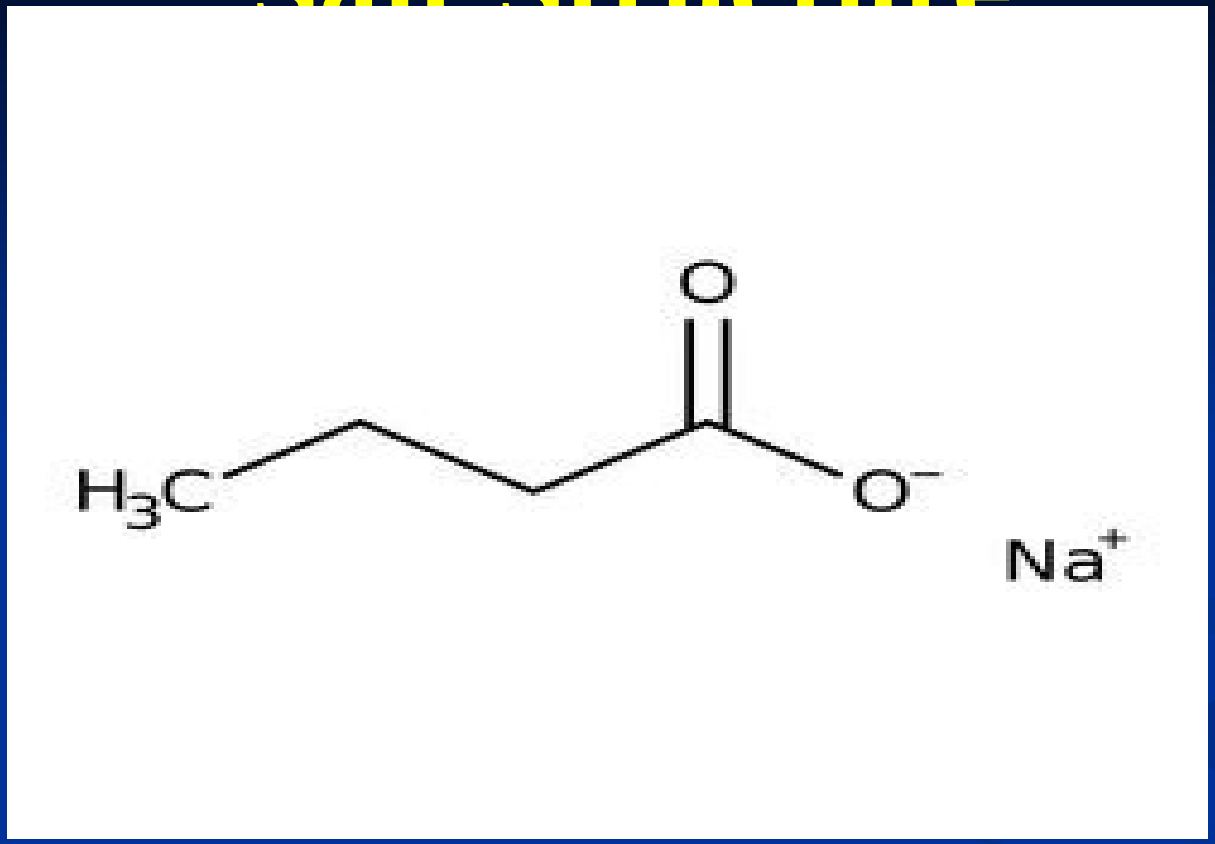
- Note that Beta-hydroxybutyrate is not literally a ketone because there is no carbon attached to an =O only attached to an R-group
- Beta-hydroxybutyrate does not function as a ketone insofar as it is converted from AcetoAcetate and to

Ketone Biochemistry



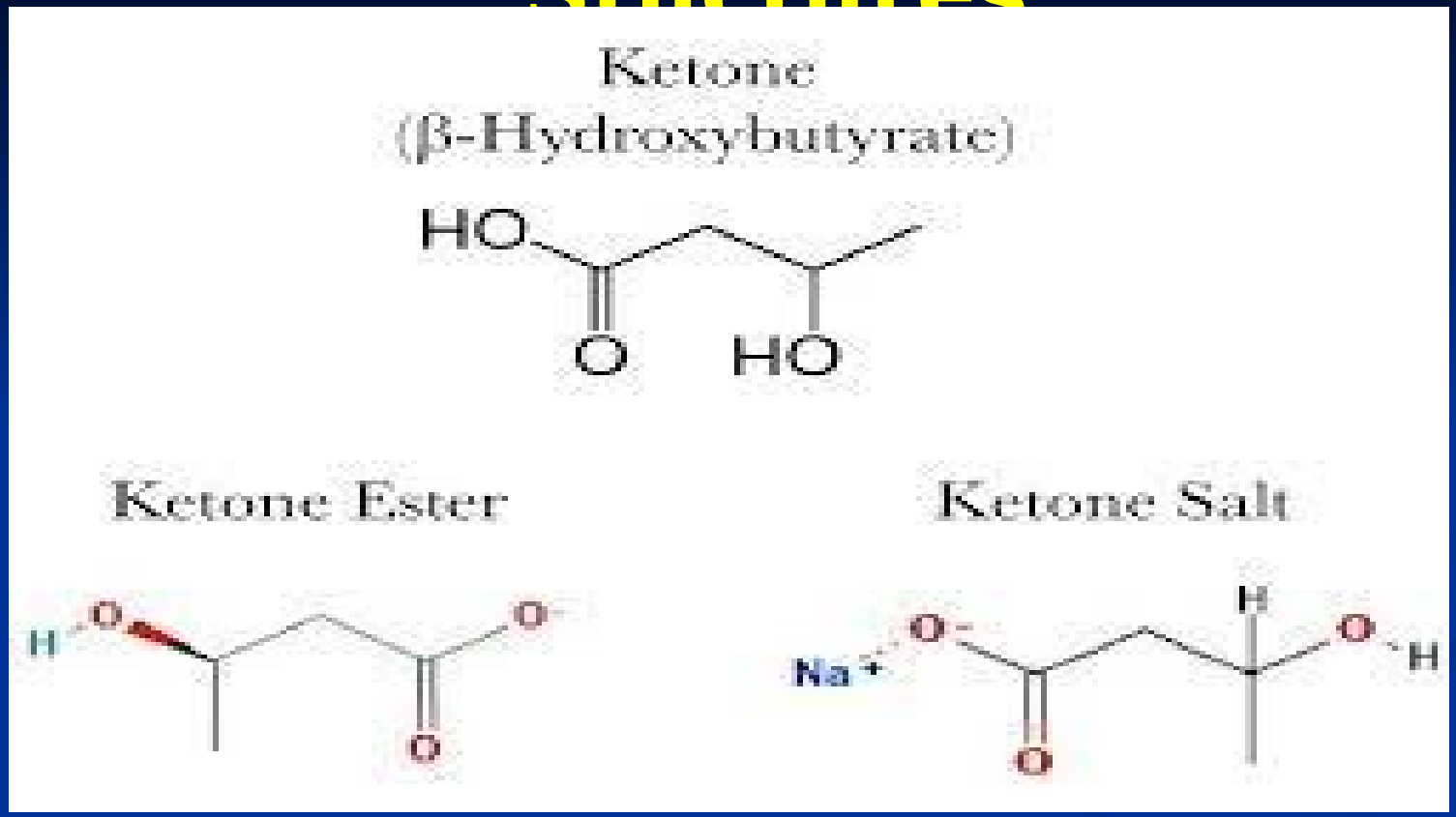
- Beta-hydroxybutyrate (βHB) made from AcetoAcetate in liver cells
- Beta-hydroxybutyrate into bloodstream by the MCT transporter
- Beta-hydroxybutyrate into non-liver cells (especially brain and skeletal muscle) by the MCT transporter

Beta-hydroxybutryrate Sodium Salt Structure



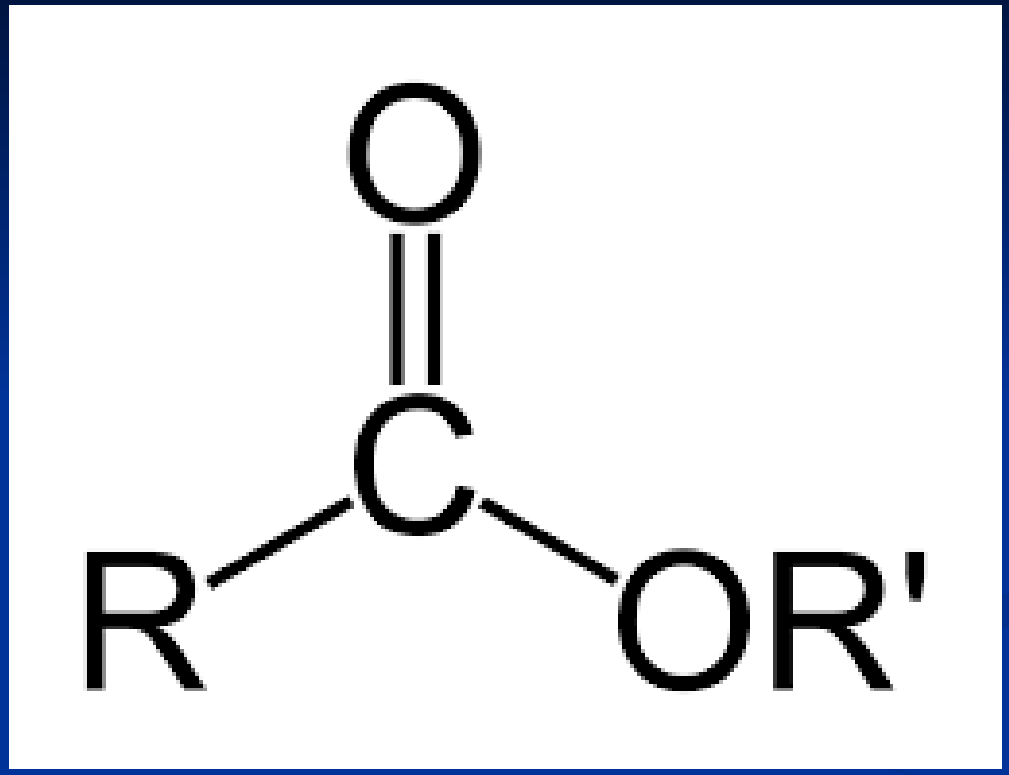
- Sodium ion dissociates from the beta-hydroxybutryrate ion

Ketone Ester versus Ketone Salt Stuctures



- Sodium Salt shown

Ketone Ester Structure



- Carbon and Oxygen atoms shown, organic groups shown as R and R’

Ketone Benefits

- In addition to being an energy source, beta-hydroxybutyrate (βHB) has protective signaling properties
- βHB lessens number of senescent cells and reduces SASP (Senescence-Associated Secretory Phenotype, which refer to toxic substances produced by senescent cells)
- βHB inhibition of histone deacetylases induces neurogenesis and protects the nervous system from NF-kB inflammation
  - NUTRIENTS 13:3420 (2021)
  - FRONTIERS IN NUTRITION 6:63 (2019)
- Ketones increase blood flow to the brain
  - THE AMERICAN JOURNAL OF PHYSIOLOGY 270:E746 (1996

Blood Ketone Levels (millimoles/Liter)

- Normal ketone levels vary between 0.1 and 0.4 mmol/L
- Nutritional ketosis defined as 0.4 to 1.0 mmol/L
- Ketogenic diet (very low carbs) typically above 2 mmol/L
- 90 minutes intense exercise can raise ketones to 1-2 mmol/L
- For weight loss 1.5-3.0 mmol/L
  - Recommended by Stephen Phinney and Jeff Volek
- Some authorities put risk ketoacidosis as low as 3.0 mmol/L for diabetics
- My ketones have reached levels above 5 mmol/L by eating butter, mayonnaise, or olive

Exogenous Ketones

Exogenous Ketone to Animals

- Exogenous ketones lower blood glucose without elevating blood lipids
  - FRONTIERS IN PHYSIOLOGY 8:848 (2017)
- βHB administered to nematode worms extends lifespan 20%
  - EXPERIMENTAL & MOLECULAR MEDICNE 52:548 (2020)
- βHB ester given to rats resulted in a 1.7-fold decrease in blood glucose and a halving of blood insulin
  - IUBMB LIFE 69:305 (2017)
- Rats fed ketone esters showed improved physical and cognitive performance
  - FASEB JOURNAL 30:4021 (2016)
- Feeding ketone esters to mice substantially increases the number of mitochondria and insulin sensitivity

Exogenous Ketone to Humans

- Ketone salts can cause a gastrointestinal stress, not seen with ketone esters, although ketone esters have a bitter taste
  - BMC MEDICINE 19:313 (2019)
- Ketone ester given to healthy young males decreased blood glucose and suppressed glucose production by about 20%
  - JOURNAL OF PHYSIOLOGY 596:1385 (2018)
- Ketone ester drinks increase blood βHB levels 50% more than ketone salt drinks
  - FRONTIERS IN PHYSIOLOGY 8:848 (2017)
- An exogenous βHB plus MCT mixture improved cognitive function in some, but not all, of a study of 13 male runners
  - NUTRITION & METABOLISM 17:81 (2020)
- Ketone ester drinks suppress appetite in

Ketone Ester Drink

- 2.5 grams ketone ester per 5 milliliters
- Bitter taste
- 3 bottles for $104.95 on Amazon
- 60 milliliters per bottle

Blood values KE4 self-administration (Ben Best, April 30, 2022) (5 mL = 2.5 grams per hour) Total cost of experiment $23.32

Hour	0	1	2	3	4	5	6	7	8
Glucose mg/dL	103	101	94	94	91	91	85	85	80
β-HB mmol/L	0.3	0.6	1.5	0.9	1.1	0.7	1.1	1.1	1.8

Ketone Ester Beverage

- 5.2 grams ketone esters per half-can
- Pleasant taste, carbonated

Blood values R 1,3 self-administration (Ben Best, May 3, 2022)
(6 fluid ounces = 5.2 grams per hour)
Total cost of experiment $33.19

Hour	0	1	2	3	4	5	6	7	8	9
Glucose mg/dL	109	98	92	88	90	81	79	76	70	72
β-HB mmol/L	0.4	1.2	1.3	1.3	1.8	1.8	2.1	1.7	2.2	2.3

Ketone Salt Powder

- 5 grams net ketone salt/half-cup in water
- Pleasant taste, no

Blood values KetoCaNa self-administration (Ben Best, May 7, 2022)
(5 grams per hour in half-cup water)
Total cost of experiment $24.50

Hour	0	1	2	3	4	5	6	7	8	9	10
Glucose mg/dL	85	82	77	71	68	64	63	67	67	69	67
β-HB mmol/L	0.7	0.8	1.9	0.9	0.9	0.9	1.4	0.6	1.4	1.6	0.9

Comments on Experiments

- I fasted for the duration of all experiments, so some drop in blood glucose and rise in blood βHB would be expected
- Note that I doubled the 2.5 grams ketones per dose given in the first experiment to 5 grams in the 2nd and 3rd experiments
- The starting levels of glucose and ketone were different in each experiment
- The ketone esters more dramatically raised blood βHB than the ketone salt, even in the first experiment which used only 2.5 grams of ketone
- The only experimental results were blood glucose and βHB, so benefits must be surmised

Concluding Remarks

- I eat many berries, which prevents my diet from being completely ketogenic
  - Blueberries protect against cardiovascular disease
    - AMERICAN JOURNAL OF CLINICAL NUTRITION 109:1535 (2019)
  - Blueberries protect against cognitive decline
    - NUTRIENTS 14:1619 (2022)
- I now believe that exogenous ketones can add to the benefit of a ketogenic diet
- I intend to drink KE4 daily in 5 mL portions
- The costs of exogenous ketones are easier to determine than the benefits
- My blood tests should show improved

QUESTIONS ???

- QUESTIONS ????